

Amendments to the Claims

Applicants respectfully request that the subject patent application be amended as follows.

1-60. (Canceled)

61. (Withdrawn) A method for isolating gamma-secretase from a sample by isolating gamma secretase complexed with PS1.

62. (Withdrawn) The method of claim 61, wherein isolating gamma-secretase complexed with PS1 comprises contacting the sample with an agent that recognizes and binds PS1 so that an agent/PS1/gamma secretase complex forms thereby isolating the molecule having gamma-secretase activity.

63. (Withdrawn) A molecule having gamma-secretase activity isolated by the method of claim 61.

64. (Withdrawn) The method of claim 62, wherein the agent that recognizes and binds PS1 comprises an anti-PS1 antibody.

65. (Withdrawn) A method for isolating a protein complex having gamma-secretase activity from a sample, comprising:

- a) contacting the sample with a molecule that recognizes and binds PS1 so that a molecule/PS1 complex forms; and
- b) removing the molecule/PS1 complex from the sample, thereby isolating the protein complex having gamma secretase activity.

66. (Withdrawn) A protein complex having gamma-secretase activity isolated by the method of claim 65.

67. (Withdrawn) The method of claim 65, wherein the molecule that recognizes and binds PS1 comprises an anti-PS1 antibody.

68. (Withdrawn) The method of claim 65, wherein the protein complex comprises gamma secretase and PS1.

69. (Withdrawn) A protein complex isolated by the method of claim 65.

70. (Withdrawn) A method for isolating a protein complex comprising gamma secretase and PS1, comprising:

- (a) solubilizing a gamma-secretase positive cell thereby resulting in a mixture of a protein complex comprising gamma-secretase and PS1 and other cell components;
- (b) contacting the mixture with a molecule that recognizes and binds PS1 so that a molecule/PS1 complex forms; and
- (c) removing the complex from the other cell components thereby isolating a protein complex comprising gamma secretase and PS1.

71. (Withdrawn) A protein complex comprising gamma secretase and PS1 isolated by the method of claim 70.

72. (Withdrawn) The method of claim 70, wherein the molecule that recognizes and binds PS1 is an anti-PS1 antibody.

73. (Withdrawn) The method of claim 70, wherein in step (a) the gamma-secretase positive cell is solubilized in a solution comprising N-[3[(dimethylamino)propyl] 3, 7, 12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide].

74. (Withdrawn) An isolated functionally-active substrate which is cleaved by gamma-secretase.

75. (Withdrawn) The functionally-active substrate of claim 74 comprising  $\beta$ APP.

76. (Withdrawn) A method for cleaving a functionally-active substrate comprising incubating the functionally-active substrate with a molecule having gamma-secretase activity under conditions so that the molecule having gamma-secretase activity cleaves the functionally-active substrate thereby producing cleavage products.

77. (Withdrawn) A method for detecting gamma-secretase activity in a molecule of interest by determining whether the molecule can cleave a substrate in accordance with the method of claim 76.

78. (Withdrawn) The method of claim 76, wherein the functionally-active substrate comprises  $\beta$ APP.

79. (Withdrawn) The method of claim 76, wherein the functionally-active substrate and the molecule having gamma-secretase activity are incubated in a solution comprising N-[3[(dimethylamino)propyl] 3, 7, 12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide].

80. (Withdrawn) A method for isolating a functionally-active substrate, comprising:

- (a) generating a substrate comprising a gamma-secretase cleavage sequence;
- (b) inserting the substrate into a microsomal membrane fragment to generate a functionally-active substrate; and
- (c) isolating the microsomal membrane fragment which includes the functionally-active substrate.

81. (Withdrawn) A functionally-active substrate generated by the method of claim 80.

82. (Withdrawn) The method of claim 80, wherein the substrate comprises  $\beta$ APP.

83. (Withdrawn) The method of claim 80, wherein the substrate comprises the amino acid sequence as described in SEQ ID NO 2 or 4.

84. (Withdrawn) The method of claim 80, wherein the functionally-active substrate includes a detectable label.

85. (Withdrawn) The method of claim 80, wherein the functionally-active substrate is solubilized from the microsomal membrane fragment with a solution comprising N-[3[(dimethylamino)propyl] 3, 7, 12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide].

86. (Withdrawn) The method of claim 80 further comprising:

- (a) solubilizing the functionally-active substrate from the microsomal membrane fragment; and
- (b) isolating the functionally-active substrate.

87. (Withdrawn) A method for identifying an agent of interest that inhibits gamma-secretase activity in a sample comprising:

- (a) contacting the sample and the agent of interest with a functionally-active substrate; and
- (b) detecting whether a cleavage product of the functionally-active substrate is generated in the sample, the lack of the cleavage product in the sample being indicative that the agent inhibits gamma-secretase activity in the sample.

88. (Withdrawn) The method of claim 87, wherein the cleavage product is detected with an antibody that recognizes and binds to the N-terminal end of the cleavage product.

89. (Withdrawn) The method of claim 87, wherein the cleavage product is detected with an antibody that recognizes and binds to the C-terminal end of the cleavage product.

90. (Withdrawn) The method of claim 87, wherein the cleavage product is detected with a pair of fluorescent adducts wherein a first fluorescent adduct binds to the N-terminal end

of the cleavage product and a second fluorescent adduct binds to the C-terminal end of the cleavage product, and wherein excitation of one of the fluorescent adducts provides a detectable transfer of energy to the other fluorescent adduct.

91. (Withdrawn) The method according to claim 87 which comprises contacting a plurality of substantially identical samples each separately with a different agent of interest.

92-94. (Canceled)

95. (Withdrawn) The method of claim 91, wherein the plurality of substantially identical samples are each contacted essentially simultaneously with a different agent of interest.

96. (Currently amended) A method for isolating a gamma secretase ~~an integral membrane~~ protein or a gamma secretase protein complex comprising:

- (a) solubilizing a cell with a solution comprising N-[3[(dimethylamino)propyl] 3, 7, 12-trihydroxy(3a, 5b, 7a, 12a)cholan-24-amide] thereby obtaining a mixture having the gamma secretase ~~integral membrane~~ protein or gamma secretase protein complex and other cell components; and
- (b) isolating the gamma secretase ~~integral membrane~~ protein or gamma secretase protein complex.

97. (Withdrawn) An integral membrane protein or protein complex isolated by the method of claim 96.